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Editorial

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Introduction

Osteoarthritis becomes an affliction for very many people worldwide at some point in their lives. Although the disease is not life-threatening it can have, nevertheless, an enormous socioeconomic impact by causing extreme discomfort and disability. Osteoarthritis has been known to mankind since its origins but now, thanks to the bold approach of surgically replacing dysfunctional joints with endoprostheses, long-term relief can be provided for many patients. However, in spite of a substantial research effort, therapeutic strategies addressed to the underlying causes are still not in sight. Why?

The term osteoarthritis is applied to a heterogeneous group of degenerative joint disorders. Some pathogenetic mechanisms result from mutations in single genes[1–4] but the majority of osteoarthritic aetiologies so far remain elusive. This holds even for the genetic causes. Nature certainly has taken some risks. The peril is that, sometimes, cartilage is a tissue meant to be permanent, most prominently so in joint cartilage. However, similar tissues serve in development, growth and repair of bones and, in these cases, the physiological destiny of cartilage is to degenerate and, eventually, to disappear. If the control mechanisms of cartilage homeostasis confuse the two situations there will be serious consequences. Is osteoarthritis, therefore, nothing but a misguided form of bone formation?

What are the molecular levers controlling cartilage development and differentiation or endochondral ossification? And what keeps articular cartilage permanent with—hopefully—minimal changes throughout life? The two questions seem to be interrelated. They stood at the centre of interest in a meeting, sponsored by Sulzer Medica, that took place in Surlej in the Engadine Valley in Switzerland. Novel and state-of-the-art treatments by orthopaedic surgery of cartilage defects were presented (Jakob *et al.*). In addition, a small group of experts in cartilage biology joined their efforts with a few specialists in tissue engineering to gain insight from the first, still insecure steps in making new joint cartilage *in vitro* and from the fate of the engineered tissue in experimental joint defects. The results are described in the following articles by Mainil-Varlet *et al.* and Weisser *et al*. What could be suitable cellular sources for such cartilage and what treatment do such cells need? This is addressed by the articles of Mastrogiacomo *et al.*, Hedbom *et al.* and Hiraki *et al*. Why is the graft cartilage sometimes integrated very well into host tissues but, unfortunately, not always? In addition, the formation of functionally inferior fibrocartilage cannot be prevented reliably. Why not?

The group has looked at these and related questions from several angles. The largest volume fraction in cartilage is occupied by the extracellular matrix which also takes over many critical tissue functions. What are the macromolecular matrix components of skeletal tissues (Segat *et al.*, Svensson *et al.*) and how can they be investigated by novel methods (Calabro *et al.*)? How is the extracellular matrix perceived at the cell surface by integrin matrix receptors (Eble)? Endochondral bone formation is affected, sometimes severely, by mutations in genes for matrix macromolecules which can occur naturally in patients with heritable connective tissue disorders. This is reviewed by Bateman. Gene alterations can also be introduced experimentally in whole animals. A number of consequences of such manipulations are visited by Aszódi *et al.*, Lefebvre *et al.*, So *et al.*, Uusitalo *et al.*, and Vortkamp which sheds new light on cartilage physiology. Not only do we learn about the functions of matrix macromolecules, but also of intra- and extracellular components of signalling cascades. Regulatory mechanisms, however, remain a major domain for cell culture studies where the consequences of experimental perturbation can be investigated most directly. Examples are given in the articles by Descalzi-Cancedda *et al.*, Enomoto-Iwamoto *et al.*, Farjanel *et al.*, Iwamoto *et al.*, Koyano *et al.*, Lefebvre *et al.*, Poliard *et al.*, and Shukunami and Hiraki. The complexity of the regulators (matrix components, extracellular signals, intracellular cascades) is revealed. There is positive and negative control of chondrocyte differentiation. It also becomes apparent that all components act in the context of each other and this fact severely complicates the interpretation of *in vitro* studies.

The meeting held in the vicinity of some of the major peaks of the Alps concluded that there still is a long way uphill towards the goal of understanding cartilage biology. The benefits of eventually achieving this goal, however, will

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be rewarding—as is the strenuous effort of reaching the summit of a tall, snow- and ice-covered mountain.

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